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Review Article

What can Neurosurgeons Do for Brain Tumor Patients: 15-Year Experience at a Cancer Center

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Abstract

Brain tumors are a diverse group of neoplasms that frequently lead to morbidity and mortality in patients. Neurosurgery is one of the mainstays in the treatment for brain tumors. With the evolution of microsurgical techniques and the advances in sophisticated equipments in past two decades, neurosurgical operations for brain tumor become much safer. In fact, neurosurgeons can provide service more than the removal of the tumor. In this article, sharing our 15-year experience at a cancer center and aimed to give some examples of what neurosurgeons can do for patients with brain tumor.

Keywords: Brain tumor; Neuronavigation; Intraoperative MRI; Interstitial therapy; Glioma-initiating cells

Abbreviations

CNS: Central Nervous System; GBM: Glioblastoma Multiforme; fMRI: Functional Magnetic Resonance Imaging; BOLD: Blood Oxygenation Level Dependent; DTI: Diffusion Tensor Imaging; iMRI: Intraoperative Magnetic Resonance Imaging; BBB: Blood-brain Barrier; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; TMZ: Temozolomide; GICs, Glioma-initiating Cells

Introduction

Brain tumors comprise a major disease in central nervous system (CNS). It is estimated that there are 22,910 new cases of brain tumors and 10,280 brain tumor-related deaths in the United States in 2012 [1]. The incidence of both primary and secondary brain tumors tends to increase in the past two decades probably due to the environmental factors, the advances in diagnostic facilities and the improvement in health care [2]. Brain tumors are composed of a variety of entities, ranging from slow-growing and curable tumors such as meningiomas and acoustic neuromas, to unlimited proliferative and devastating ones such as glioblastoma multiforme (GBM) and brain metastases [3]. Neurosurgical procedure is usually the first and important step in the treatment of brain tumors. Neurosurgeons play an important role in the treatment of brain tumors. In this article, we are sharing our 15-year experience at the scenario of Sun Yat-sen University Cancer Center with "state-of-arts neurosurgery", and discuss what a neurosurgeon can do for brain tumor patients.

Resection with safety

Safe removal to cure brain tumor or reduce tumor burden is the primary goal of neurological operation under most circumstances. We personally operated for around 3000 cases of brain and spinal tumors during last 15 years at Sun Yat-sen University Cancer Center. Roughly 50% cases were benign tumor such as meningiomas, pituitary adenomas, acoustic neurinoma, and of course surgical removal is the most important job of neurosurgeons.

Keep in mind, maximum resection with minimum damage of neurological function is the golden rule for every neurosurgeon [4]. Thanks to the microsurgical concepts and the emergence of sophisticated equipments, the neurological surgery becomes more and more safe. Pre-operative functional magnetic resonance imaging (fMRI) techniques, such as blood oxygenation level dependent (BOLD) imaging and diffusion tensor imaging (DTI), are used to identify eloquent brain areas, and trace subcortical fiber tracks and tumor infiltration, which helps planning the approach and resection strategy [5]. We analyzed DTI data of 38 cases with glioma and assessed the neurological function of these patients before and after surgery. According to DTI, the relationship between glioma and the adjacent white matter tracts can be classified as Type I, displacement; Type II, infiltration; Type III, disruption. We demonstrated that the pre- and post-operative neurological function is highly related to the pattern of glioma growth and DTI is a useful tool to make operation plan and guide the surgery [6].

Intraoperative neuronavigation allows visualizing the tumor and critical structures around it for guidance during the surgery [7]. Awake craniotomy and intraoperative cortical mapping are critical and necessary for safe surgery in brain functional areas. The electronic stimulation facilitates to locate areas where motor, language, or visual functions are seated [8]. The introduction of intraoperative MRI (iMRI) into operation is a breakthrough in the field of neurosurgery. iMRI can provide the real-time source image used for navigation system, which eliminates the error resulted from the brain shift due to the loss of cerebrospinal fluid and tumor resection [9]. Level 2 evidence supports that iMRI-integrated neurosurgery is more effective in increasing the extent of total resection, improving quality of life, or prolonging survival in patients with brain tumor, compared to conventional neuronavigation-guided surgery [10].

Local therapy

Brain is a unique organ with special anatomy and physiology. One of the differences in anatomical features to other organs is the existence of the blood-brain barrier (BBB). The BBB, which is formed by a network of endothelial cells, pericytes and astrocyte processes, shelters the brain from many bacterial infections and neurotoxins

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[11]. However, the protection of BBB is a double-blade sword, which can also limit the entrance of many antitumor chemotherapeutic agents into CNS. As a result, only a few cytotoxic drugs can be effectively administered through systemic methods for the treatment of malignant brain tumors [12]. Neurosurgeons have the unique opportunity to bypass BBB by directly exposing the tumor bed after resection. Interstitial chemotherapy is therefore a promising strategy to deliver drugs. Gliadel wafers, containing the active antiglioma agent BCNU, are currently the most successful local delivery system for malignant gliomas [13]. Systemic reviews have revealed the safety and effectiveness of Gliadel wafers in the treatment of GBM [14]. Gliadel wafers are therefore recommended to be integrated into the management for malignant gliomas. But until now, no local delivery system is commercially available in China. To fulfill this blank, we carried out a Phase I trial to evaluate the safety of a high-dose BCNU-loaded implant, developed by a Chinese pharmaceutical company, in patients with recurrent malignant gliomas. We enrolled a total of 15 patients and found that up to 12 implants impregnated with 240 mg of BCNU are well tolerated in the enrolled patients [15]. The phase II/III trial is ongoing to test the efficacy of the high-dose BCNU-loaded implant.

Immunotherapy for glioma has been traditionally viewed as the underdog among the treatment modalities because gliomas grow in the sanctuary of brain, which is protected from infiltrating immune executors and there are various mechanisms glioma cells can employ to escape the immune surveillance [16]. However, with the improvement understanding of the glioma biology and human immune system, and with the advances in techniques of molecular biology, a variety of strategies have been develop to initiate and enhance the host immune activity against glioma [17]. The introduce of effective immune killers to the tumor bed is one of them. In one of our studies, we placed an Ommaya reservoir into the tumor bed at the craniotomy in a cohort of 6 patients with malignant glioma. After radiation and chemotherapy, the patients received series of intracranial injection of cytokine-induced killer cells through Ommaya reservoir. We demonstrated that the local immunotherapy is generally safe. Efficacy of the treatment was observed. Among 6 patients, complete response (CR) was found in 2 cases, partial response (PR) in 1 case, stable disease (SD) in 1 case and progressive disease (PD) [18].

Primary culture from tumor tissues

The established brain tumor cell lines, such as U87 and U251, are the most widely used preclinical tools to investigate the tumor biology and test strategies against brain tumor. Although the established brain tumor cell lines have many advantages such as stability and reproducibility, the drawbacks are obvious. It is well documented that the established cell lines kept in serum-containing medium acquired molecular changes and lose the tissue-specific features in the process of immortalization [19]. Differences in genotype and phenotype between the established cell lines and the original tumors are frequently found. This can partially explain why the preclinical successful results generated from the established cell lines fail to translate into clinical efficacy. Preclinical models with tumor cells which can mirror their origin are pivotal in biomedical research. Primary culture from tumor tissues is one of the approaches to overcoming the disadvantages of the established cell lines. As neurosurgeons, we can access to the fresh tumor tissues at the first time and utilize them for culture. We have employed primary cell culture to test the sensitivity of glioma to chemotherapeutic drugs for more than 1000 samples. We found that the sensitivity detected with primary culture is consistent with molecular characteristics of the parental tumors, such as MGMT status, microRNA level and ERCC1 promoter hypermethylation [19-21]. Most importantly, the preclinical data were correlated with the clinical response to cytotoxic agents, which is very helpful in formulating chemotherapy regimens before the era of temozolomide (TMZ) [22].

Glioma-initiating cells (GICs) are another ideal model for brain tumor research. GICs are isolated from freshly resected glioma and maintained under serum-free conditions. GICs have a very strong capacity to initiate tumors *in vivo* and have been shown to keep both the genetic and phenotypic features of the derived tumors even after repeated passage [23]. We established several GIC lines and used them to test our hypothesis and new strategies against gliomas. For example, we revealed that GICs are capable of vasculogenesis through vascular mimicry, an alternative microvascular circulation independent of endothelial cell angiogenesis, which is a potential target for glioma treatment [24]. We also demonstrated that valproic acid, the widely used anti-seizure drugs, induces autophagy in GICs through oxidative stress and enhances autophagic death triggered by TMZ [25]. In addition, we showed for the first time that triptolide, an extract from the Chinese herb Triptergium wilfordii hook; potentates TMZ-induced apoptosis through inhibit NF-κB signaling [26]. With the model of GICs, we provide some insight on the potential target or strategy for the treatment of glioma.

Conclusion

From our 15 years experience working at a Cancer Center, we can conclude that neurosurgeons can do more besides the removal of brain tumors. We are surgical neuro-oncologist and thus can do local neuro-oncology job, such as, local delivery of therapeutic agents. Fresh tumor tissue can be more important than just diagnostic samples, but also study materials. Actually, many laboratory investigations should be close collaborated with neurosurgeons so that to make study available, for example, accurate sampling of the tumor tissues. Many tumors in central nervous system are still disaster, and explorations of novel strategies to improve the prognosis of the patients are our ultimate goals. We should keep in mind Neurosurgeon can do for brain tumor patients, not just surgery, but "state-of-art" work.

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